REMARKS

Status Summary

Claims 1-50 are pending. Claims 22-23, 36-37 are withdrawn from consideration, and claims 1-21, 24-35, and 38-50 were examined. Claims 1-21, 24-35, and 38-50 are rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to teach one skilled in the art how to make and/or use the invention. Claims 1-2, 9-15, 24-30, 38-42, and 48-50 are rejected under 35 U.S.C. § 112, first paragraph, as allegedly lacking written description of the claimed invention. Claims 6, 19, 33, and 43 are rejected under 35 U.S.C. § 112, second paragraph, as allegedly indefinite. Claims 1-21, 24-35 and 38-50 are rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over U.S. Patent No. 6,403,091 to Lederman et al. in view of U.S. Patent No. 5,597,563 to Berschorner et al. and U.S. Patent No. 6,056,956 to Cobbold et al. Claims 1-21, 24-35 and 38-50 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-34 of U.S. Patent No. 5,683,693, claims 1-34 of U.S. Patent No. 5,902,585, and claims 1-7 of U.S. Patent No. 6,375,950.

Claims 2-3 and 16 are canceled. Claims 1, 4-5, 12, 15, 17-18, 27, 30, and 41-42 are amended as indicated above. Reconsideration in view of the amendments and following remarks is respectfully requested.

Objections to the Specification

The examiner requests amendment of the specification (1) to update the status and relationship of the priority documents, and (2) to properly referenced trademarked materials. Office Action, page 2, items 4-5. The specification is amended accordingly. Withdrawal of the objections to the specification is respectfully requested.

Rejection of Claims Under 35 U.S.C. § 112, First Paragraph (Enablement)

Claims 6, 19, 33, and 43

Claims 6, 19, 33, and 43 are rejected based on the perceived unavailability of the MR1 antibody. Office Action, page 3, item 7. This rejection is respectfully traversed.

The hybridoma identified in this application as MR1 was deposited on May 22, 1992 with the American Type Culture Collection, P.O. Box 1549, Manassas, Virginia, 20108, in compliance with the Budapest Treaty, and accorded Accession Number ATCC HB 11048. The specification as originally filed identifies MR1 as corresponding to the HB11048

hybridoma at page 18, lines 26-28. The specification is amended herein to clearly state public accessibility to the deposited cell line. Based thereon, claims 6, 19, 33, and 43 are believed to fully comply with the requirements of § 112, first paragraph, and withdrawal of the rejection of claims 6, 19, 33, and 43 is respectfully requested.

Based on the foregoing, claims 6, 19, 33, and 43 are believed to fully enable practice of the invention as required under 35 U.S.C. § 112, first paragraph. Therefore, applicants respectfully request withdrawal of this rejection of claims 6, 19, 33, and 43.

Rejection of Claims Under 35 U.S.C. § 112, First Paragraph (Enablement)

Claims 1-2, 9-15, 24-30, 38-42, and 48-50

Claims 1-2, 9-15, 24-30, 38-42, and 48-50 are rejected based on the examiner's contention that the specification, while enabling for the use of anti-gp39 / anti-CD40 ligand antibodies, does not reasonably provide enablement for the use of any receptor antagonist or a gp39 antagonist to induce T cell tolerance or nonresponsiveness. Office Action, pages 5-7, item 9. This rejection is also respectfully traversed.

Claim 1 is directed to methods for inducing T cell tolerance via administration of an anti-gp39 antibody, as originally set forth in claim 3, now canceled. Claims 12, 27, and 41 are amended to reflect proper antecedent basis. Claim 2 is also canceled, and thus the rejection of claim 2 is rendered moot. Claims 9-15 and 24-29 ultimately depend from claim 1 and also include the use of an anti-gp39 antibody.

Claim 30 is directed to a method for treating diabetes via administration of an anti-gp39 antibody. Claims 38-41 ultimately depend from claim 30, and thus also include the use of an anti-gp39 antibody.

Originally filed claim 42 is directed to a method for inducing T cell tolerance to a donor tissue or organ in a recipient of the tissue or organ via administration of an anti-gp39 antibody. Claim 42 does not include a receptor antagonist or a gp39 antagonist, which language serves as the basis for the examiner's rejection. Claims 48-50 ultimately depend from claim 42 and thus also include the use of an anti-gp39 antibody.

Based on the foregoing, claims 1, 9-15, 24-30, 38-42, and 48-50 are believed to fully enable use of the invention as required under 35 U.S.C. § 112, first paragraph. Thus, applicants respectfully request withdrawal of the rejection of claims 1, 9-15, 24-30, 38-42, and 48-50.

Rejection of Claims Under 35 U.S.C. § 112, First Paragraph (Enablement)

Claims 1-21, 24-35, and 38-50

Claims 1-21, 24-35, and 38-50 are further rejected under 35 U.S.C. § 112, first paragraph, on the basis that there is insufficient nexus of the use of gp39-specific antagonists and antigen-presenting cells to accomplish the therapeutic endpoint of tolerance. The examiner contends that while anti-gp39 antibodies have been used to induce immunosuppression, induction of immunological tolerance has not been clearly demonstrated. The examiner further argues that a skilled artisan would not readily extrapolate an ability to induce immunological tolerance in murine model organisms to a similar ability in humans and that induction of tolerance in humans would require undue experimentation. In support of this contention, the examiner cites Auchincloss (1995) in Bach & Auchincloss (eds), Transplantation Immunology, Wiley Liss, New York, pp. 211-18, which suggests that the development of methods for inducing tolerance in humans has lagged behind promising studies in smaller animals. Office Action, pages 7-8, item 10. This rejection is respectfully traversed.

Enablement "is not precluded even if some experimentation is necessary, although the amount of experimentation needed must not be unduly excessive." *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1384, 231 USPQ 81, 94 (Fed. Cir. 1986). The test [for undue experimentation] is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed to enable the determination of how to practice a desired embodiment of the claimed invention. *PPG Indus., Inc. v. Guardian Indus. Corp.*, 75 F.3d 1558, 1564, 37 USPQ2d 1618, 1623 (Fed. Cir. 1996) (quotation and citation omitted). In *Johns Hopkins Univ. v. CellPro,* 152 F.3d 1342 (C.A.Fed. (Del.) 1998), the Court of Appeals for the Federal Circuit rejected appellants' argument that methods for producing CD24 antibodies were generally "more difficult" than other monoclonal antibodies as sufficient to show lack of enablement.

The examiner bears the initial burden to set forth reasonable explanation as to why it believes that scope of protection provided by claim is not adequately enabled by description of invention in specification of patent application. Applicants respectfully submit that the examiner has failed to meet this initial burden.

Applicants initially respond that, contrary to the examiner's contention, anti-gp39 antibodies can be used to induce immunological tolerance in accordance with the examiner's definition of tolerance as a long-lasting nonreactivity of the immune system to a specific set for antigens, which is maintained without continued immunosuppression. Example 1 of the instant specification describes induction of tolerance to pancreatic islet allografts by treatment of the graft recipient with allogeneic cells and an anti-gp39 antibody. As disclosed therein, the combined administration of allogeneic spleen cells and anti-gp39 was found to be more effective than either reagent alone. Indefinite graft survival was achieved in all animals treated for 7 weeks with anti-gp39 and a single injection of Fraction 19 APC depleted spleen cells, which supports that gp39 is an effective immunosuppressant. Indefinite graft survival was also achieved following administration of anti-gp39 for only 2 weeks in combination with Fraction 19 APC depleted spleen cells. Thus, graft recipients showed immunological tolerance to the allogeneic cells without continued immunosuppression. *See e.g.*, pages 15, line 30, through, page 16, line 8 and Figure 2.

Applicants further respond that the failed attempts to develop methods for inducing tolerance in humans, as described by Auchincloss, are ancillary to present requirement because the methods described therein are distinct from the methods of the present invention. Because the cited reference deviates from the teachings of the instant application, Auchincloss is insufficient to raise a serious doubt that the instant methods are nonenabling. The examiner has not pointed to any evidence that indicates how the methods presently claimed are not enabled by the instant specification. The examiner's reference to Auchincloss, without explanation of how that reference bears on the methods of the present invention, fails to satisfy the burden of establishing a reasonable doubt as to why the present claims are believed to be nonenabled.

Applicants further respond that the difficulty alleged by Auchincloss does not refute successes in inducing tolerance in humans accomplished by other researchers. *See e.g.*, Norman et al. (1996) *Am J Respir Crit Care Med* 154:1623-8; Fukaura (1996) *J Clin Invest* 98(1):70-7 (administration of myelin basic protein to human patients with multiple sclerosis induces circulating mylein basic protein-specific Th3 T cells); Weiner et al. (1994) *Annu Rev Immunol* 12:809-37 (oral administration of antigen is long recognized method for inducing peripheral immune tolerance); Moreland et al. (1993) *Arthritis Rheum* 36:307-318 (administration of anti-CD4 antibody to human patients with refractory rheumatoid arthritis

depresses T cell responses); Varney et al. (1993) *J Clin Invest* 92:644-651 (grass pollen immunotherapy in human patients with hay fever suppresses allergen-induced T cell infiltration); Trentham (1993) *Science* 261(5129):1727-30 (administration of type II collagen to human patients with active rheumatoid arthritis results in fewer swollen joints and/or complete remission). In accordance with *Johns Hopkins Univ. v. CellPro*, the "difficulty" alleged by one artisan (Auchincloss) among the successes of others is insufficient to demonstrate a lack of enablement.

Claims 2, 3, and 16 are canceled. Thus, the rejection of these claims is rendered moot.

Based on the foregoing arguments, claims 1, 4-15, 17-21, 24-35, and 38-50 are believed to fully enable practice of the invention as required under 35 U.S.C. § 112, first paragraph. Therefore, applicants respectfully request withdrawal of this rejection of claims 1, 4-15, 17-21, 24-35, and 38-50.

Rejection of Claims Under 35 U.S.C. § 112, First Paragraph

(Written Description)

Claims 1-2, 9-15, 24-30, 38-42, and 48-50 are rejected under 35 U.S.C. § 112, first paragraph, as allegedly lacking written description of the claimed invention. Specifically, the examiner contends that any "antagonist of the receptor on the surface of the T cell which inhibits the interaction of the ligand with the receptor" or a "gp39 antagonist" are not sufficiently described. Office Action, pages 3-5, item 8. This rejection is respectfully traversed.

As noted herein above, claims 1 and 30 are directed to methods employing an anti-gp39 antibody. Claims 9-15, 24-29 and 38-41 depend from claims 1 and 30, respectively, and thus also include an anti-gp39 antibody. Original claim 42, and claims 48-50 which depend therefrom, similarly include an anti-gp39 antibody. Thus, claims 1, 9-15, 24-30, 38-42, and 48-50 are believed to fully describe the claimed invention in accordance with the requirements of § 112, first paragraph, and withdrawal of the rejection of claims 1, 9-15, 24-30, 38-42, and 48-50 is respectfully requested. Claim 2 is canceled, and thus this rejection is rendered moot.

Rejection of Claims Under 35 U.S.C. § 112, Second Paragraph

Claims 6, 19, 33, and 43 are rejected under 35 U.S.C. § 112, second paragraph, as allegedly indefinite in recitation of "MR1" because its characteristics are unknown. Office

Action, page 8, item 11. Claims 6, 19, 33, and 45 are amended to include the HB11048 hybridoma deposited with the ATCC. Originally filed claim 43 does not include an MR1 antibody. The specification as originally filed identifies MR1 as corresponding to the HB11048 hybridoma at page 18, lines 26-28.

Based on the foregoing, claims 6, 19, 33, 43, and 45 are believed to fully comply with the requirements of 35 U.S.C. § 112, second paragraph, and withdrawal of the rejection of claims 6, 19, 33, and 43 is respectfully requested.

Rejection of Claims Under 35 U.S.C. § 103(a)

Claims 1-21, 24-35 and 38-50 are rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over U.S. Patent No. 6,403,091 to Lederman et al. (Lederman) in view of U.S. Patent No. 5,597,563 to Berschorner et al. (Berschorner) and U.S. Patent No. 6,056,956 to Cobbold et al. (Cobbold). In the view of the examiner, it would have been obvious "to provide methods of providing an environment conducive to tolerance or specific unresponsiveness by combining an immunosuppressant such as the CD40L-specific antibodies, taught by Lederman et al. [w]ith a source of alloantigen or xenoantigen, as taught by Berschorner and Cobbold et al. [t]o transplant a variety of tissues and cells. Office Action, pages 9-10, item 13. This rejection is respectfully traversed.

The examiner bears the burden of presenting a *prima facie* case for obviousness, with a showing of such *prima facie* obviousness requiring: (1) some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings; (2) the teaching or suggestion of all the claim limitations of the applicant's invention in the combined prior art references; and (3) a reasonable expectation of success. MPEP § 2143. Applicants respond that the examiner has failed to meet this burden.

With regard to the first of these factors, suggestion or motivation to combine, such motivation may be found "where there is some teaching, suggestion, or motivation ... either explicitly or implicitly in the references themselves or in the knowledge generally available to one of ordinary skill in the art." MPEP § 2143.01 (citing *In re Kotzab*, 217 F.3d 1365, 1370 55 USPQ2d 1313, 1317 (Fed. Cir. 2000)). Not only must such motivation be present, "there must be some teaching, suggestion or motivation in the prior art to make the specific combination that was made by the applicant." *In re Dance,* 160 F.3d 1339, 1343, 48 USPQ2d 1635, 1637 (Fed. Cir. 1998) (emphasis added) (citing *In re Raynes,* 7 F.3d 1037, 1039, 28

USPQ2d 1630, 1631 (Fed. Cir. 1993); *In re Oetiker,* 977 F.2d 1443, 1445, 24 USPQ2d 1443, 1445 (Fed. Cir. 1992).

The fact that the prior art teaches individual elements of the claimed invention that are generally known or within the capabilities of one with knowledge in the art is not, however, sufficient to establish a *prima facie* case of obviousness without any specific teaching or suggestion for making the combination. Accordingly, in a proper analysis of obviousness, the level of knowledge of one with ordinary skill in the art cannot be substituted for a clear suggestion to make a combination. *See A-Site Corp. v. VSI International Inc.,* 174 F.3d 1308, 50 USPQ2d 1161 (Fed. Cir. 1999).

Therefore, the examiner is required to show how and why the applicant would have been motivated to combine the references in the manner combined by the examiner. The examiner has not done so, but has simply made unsupported statements regarding the alleged motivation of a person of ordinary skill in the art to undertake the components of the claimed invention. In the instant application, the examiner states that "[a] person of ordinary skill in the art would have been motivated to produce this resultant therapeutic regiment to provide an environment conducive to tolerance or specific unresponsiveness to decrease the rejection of the transplanted tissue or organ and to increase the survival of such transplants." Office Action, page 10. Despite this general recognition of a need to promote graft acceptance and survival, the cited references, whether considered alone or in combination, lack any suggestion or motivation to make the specific combination of the presently claimed invention.

Lederman describes that various immune responses can be inhibited using 5C8-specific antibodies, for example to inhibit the rejection of transplanted tissues. The examiner notes that Lederman differs from the claimed invention by not disclosing the use of additional allogeneic or xenogeneic cells. Lederman does not describe induction of tolerance. Specifically, Lederman fails to show nonreactivity of the immune system to a specific set for antigens, which is maintained without continued immunosuppression. Indeed, Lederman only describes immune cells in culture.

Berschorner describes methods for inducing antigen-specific immune tolerance by providing antigen presenting cells containing the antigen to which specific tolerance is desired, including alloantigens and xenoantigens, in combination with an immunosuppressant agent having an ability of depleting dendritic cells in the recipient's thymic medulla.

Berschorner does not describe the use of antibodies lacking an ability to deplete thymic dendritic cells, such as an anti-gp39 antibody.

Cobbold describes methods for tolerance induction using an antigen and an immunosuppressant comprising nondepleting CD4 and CD8 antibodies. Cobbold describes that the methods can be used to prevent graft rejection in tissue and organ transplants. Cobbold does not teach or suggest the use of an anti-gp39 antibody as an immunosuppressant. Rather, the use of nondepleting CD4 and CD8 antibodies is material to Cobbold's method.

The present invention provides methods for inducing T cell tolerance to a donor tissue or organ, including pancreatic islet cells in the treatment of diabetes, via administration of an anti-gp39 antibody in combination with allogeneic or xenogeneic cells. The cited references do not provide a specific teaching, suggestion, or motivation to administer anti-gp39 antibodies and allogeneic or xenogeneic cells to a subject to thereby induce tolerance, as now claimed. Thus, applicants submit that the examiner has failed to meet the burden of establishing a *primae facie* case.

Claims 1, 15, 30, and 42 are directed to methods that employ a composition comprising an anti-gp39 antibody to thereby induce tolerance. Claims 4-14 ultimately depend from claim 1, claims 17-20 and 24-29 ultimately depend from claim 15, claims 31-35 and 38-41 ultimately depend from claim 30, and claims 43-50 ultimately depend from claim 42. Thus, each of claims 4-14, 17-20, 24-29, 31-35, 38-41, and 43-50 also include an anti-gp39 antibody and induction of T cell tolerance.

Claims 2-3 and 16 are canceled, and the rejection of these claims is thereby rendered moot. Claims 4-5 and 17-18 are amended to depend from non-canceled claims.

Based on the foregoing arguments, applicants believe that claims 1, 4-15, 17-21, 24-35 and 38-50 comply with the requirements of 35 U.S.C. § 103(a), and applicants request that the rejection of claims 1, 4-15, 17-21, 24-35 and 38-50 under § 103(a) be withdrawn.

Rejection of Claims Based on Non-Statutory
Obviousness-Type Double Patenting

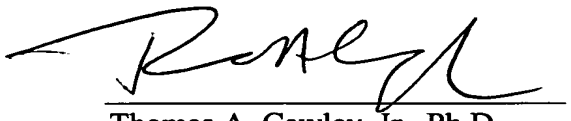
Claims 1-21, 24-35 and 38-50 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-34 of U.S. Patent No. 5,683,693, claims 1-34 of U.S. Patent No. 5,902,585, and claims 1-7 of U.S. Patent No. 6,375,950. Office Action, page 11, items 15-16. Applicants respond that a terminal disclaimer will be filed when one or more pending claims is in condition for allowance.

Conclusion

All rejections having been addressed, it is respectfully submitted that the present application is in condition for allowance and a Notice to that effect is earnestly solicited. If any points remain in issue, which the examiner feels may be best resolved through a personal or telephone interview, he is kindly requested to contact the undersigned attorney at the telephone number listed below.

Respectfully submitted,

PILLSBURY WINTHROP LLP



Thomas A. Cawley, Jr., Ph.D.
Registration No. 40,944

1600 Tysons Boulevard
McLean, VA 22102
(703) 905-2144 Direct Dial
(703) 905-2500 Facsimile

Date: April 14, 2003

TAC/JB/af